

510(k) SUBSTANTIAL EQUIVALENCE DETERMINATION
DECISION SUMMARY

A. 510(k) Number:

K132909

B. Purpose for Submission:

Addition of Tigecycline to the BD Phoenix Gram negative ID/AST and AST only panels.

C. Measurand:

Tigecycline 0.25-16 µg/mL

D. Type of Test:

Antimicrobial Susceptibility Test (Quantitative) colorimetric, oxidation-reduction, growth based

E. Applicant:

Becton, Dickinson and Company

F. Proprietary and Established Names:

BD Phoenix™ Automated Microbiology System

G. Regulatory Information:

1. Regulation section:

21 CFR 866.1645 – Short-Term Antimicrobial Susceptibility Test System

2. Classification:

Class II

3. Product code:

LON – System, Test, Automated, Antimicrobial Susceptibility, Short Incubation

4. Panel:

83 Microbiology

H. Intended Use:

1. Intended use(s):

The BD Phoenix™ Automated Microbiology System is intended for in vitro rapid identification (ID) and quantitative determination of antimicrobial susceptibility by minimal inhibitory concentration (MIC) of most Gram negative aerobic and facultative anaerobic bacteria belonging to the family Enterobacteriaceae and Non-Enterobacteriaceae.

2. Indication(s) for use:

The BD Phoenix™ Automated Microbiology System is intended for in vitro quantitative determination of antimicrobial susceptibility by minimal inhibitory concentration (MIC) of most Gram-negative aerobic and facultative anaerobic bacterial isolates from pure culture for *Enterobacteriaceae* and Non-*Enterobacteriaceae* and most Gram-positive bacteria isolates from pure culture belonging to the genera *Staphylococcus*, *Enterococcus* and *Streptococcus*.

This premarket notification is for the addition of the antimicrobial agent Tigecycline at concentrations of 0.25 - 16µg/mL to Gram-negative ID/AST or AST only Phoenix panels. Tigecycline has been shown to be active *in vitro* against most strains of microorganisms listed below, as described in the FDA-approved package insert for this antimicrobial agent.

Active In Vitro and in Clinical Infections Against:

<i>Citrobacter freundii</i>	<i>Klebsiella oxytoca</i>
<i>Enterobacter cloacae</i>	<i>Klebsiella pneumoniae</i>
<i>Escherichia coli</i>	

Active In Vitro

Serratia marcescens
Citrobacter koseri
Enterobacter aerogenes

3. Special conditions for use statement(s):

For prescription use only

4. Special instrument requirements:

For use with the BD Phoenix™ Automated Microbiology System

I. Device Description:

The BD Phoenix™ Automated Microbiology System includes instrumentation and software, sealed and self-inoculating molded polystyrene trays with 136 micro-wells containing dried reagents, and specific inoculum broth formulations for identification (ID) and antimicrobial susceptibility testing (AST). The organism to be tested must be in pure culture and preliminarily identified as Gram-positive or Gram-negative. Colonies are then suspended in the ID broth, and, using one of the recommended BD nephelometer devices, brought to a concentration of 0.5 McFarland. A further dilution is made into the AST broth. Prior to inoculation of the panel, an AST broth indicator is added which changes the AST broth to a blue color. The AST broth is a cation-adjusted formulation of Mueller-Hinton broth containing 0.01% Tween 80, and has a final isolate concentration of approximately 5×10^5 CFU/mL. After inoculation and incubation, the AST broth indicator in the AST broth changes from blue to pink to colorless as organism growth and reduction in the panel well occurs. Inoculated panels are barcode scanned and loaded into the BD Phoenix™ Automated Microbiology System instrument where the panels are incubated at 35°C and continuously measured for changes to the indicator and bacterial turbidity to determine bacterial growth in the presence of an antimicrobial agent. Organisms killed or inhibited by a given antimicrobial do not cause reduction of the indicator and therefore do not produce a color change. Additional interpretation is done using the software driven “EXPERT” System triggered rules derived from the CLSI standards and/or FDA drug labeling. Readings are taken every 20 minutes and a final AST result in 4 to 16 hours. The AST result is determined via automated readings; no manual readings are possible with this system.

J. Substantial Equivalence Information:

1. Predicate device name(s):

Vitek® Antimicrobial Susceptibility Test System

2. Predicate 510(k) number(s):

N50510

3. Comparison with predicate:

Table 1. Similarities and Differences of the BD Phoenix Tigecycline and the Predicate

Similarities		
Item	Device	Predicate
	BD Phoenix Automated Microbiology System (Tigecycline)	VITEK (N50510)
Intended Use	Determination of in vitro antimicrobial susceptibility testing of aerobic and facultative anaerobic Gram-negative and Gram-positive bacteria	Same
Source of Microorganisms for Testing	Bacterial colonies isolated from culture	Same
System	Automated instrumentation for in vitro antimicrobial susceptibility testing (AST)	Same
Incubation Time	Short-term (<16 hours)	Same
Test Card	Contains dried antimicrobials and substrates	Same
Results	MIC and Interpretive Criteria (i.e., Susceptible, Intermediate, Resistant and Non-Susceptible)	Same
Methodology	Determination of MIC using serial two-fold dilution format	Same
Technology	Automated growth-based detection	Same

Differences		
Item	Device	Predicate
Methodology	MIC determination based on serial two-fold dilution format	MIC determination based on computer assisted extrapolation of doubling dilutions
Technology	Automated growth based, enhanced by use of a redox indicator (colorimetric oxidation-reduction) to detect organism growth	Automated growth based detection using attenuation of light measured by an optical scanner

K. Standard/Guidance Document Referenced (if applicable):

- CLSI M7-A8 “Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria that Grow Aerobically”
- CLSI M100-S22 “Performance Standards for Antimicrobial Susceptibility Testing”
- Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test Systems; Guidance for Industry and FDA

L. Test Principle:

The BD Phoenix™ Automated Microbiology System is a broth based microdilution method that utilizes a redox indicator (colorimetric oxidation-reduction) to enhance detection of organism growth. The MIC is determined by comparing growth in wells containing serial two-fold dilutions of an antibiotic to the growth in “growth control wells” that contain no antibiotic.

M. Performance Characteristics (if/when applicable):

1. Analytical performance:

a. Precision/Reproducibility:

Reproducibility testing using inocula prepared manually and standardized using the PhoenixSpec nephelometer was conducted at three external sites. Ten isolates with on-scale MIC values as predetermined by reference methods were provided to the testing sites by BD. Isolate identification and expected MIC result was blinded to those conducting the testing. Testing was performed in triplicate on three separate days.

Reproducibility testing using inocula prepared by the Phoenix AP instrument was conducted at two external sites and one internal site. Testing was conducted using 16 isolates with on-scale MIC values. Isolate identification and expected MIC result was blinded to those conducting the testing. Testing was performed in triplicate on three separate days.

Results of the inter-site and intra-site reproducibility studies were acceptable and demonstrated best case and worst case results of greater than 95%. A summary of the reproducibility study performance is illustrated in Table 2 below.

Table 2. Summary of Reproducibility Studies – BD Phoenix Tigecycline

BD Phoenix Instrument Platform	Inoculation Method	Best Case	Worst Case
BD Phoenix	AP Instrument	100%	97.0%
	Manual	99.6%	97.4%

Best case calculation for reproducibility assumes off-scale results are within one well of the mode MIC value. Worst case calculation for reproducibility assumes off-scale results are greater than one well from the mode MIC value.

Regarding the manual inoculation method, best case, 1 MIC result was off-scale; worst case, 7 MIC results were off-scale. There were a total of 270 MIC values evaluated.

Regarding the automated inoculation method (AP Instrument), best case, no MIC results were off-scale; worst case 13 MIC results were off scale. There were a total of 432 MIC values evaluated.

b. Linearity/assay reportable range:

Not applicable

c. Traceability, Stability, Expected values (controls, calibrators, or methods):

The FDA and CLSI recommended quality control (QC) isolate, *E. coli* ATCC 25922 was each day of the challenge and clinical study testing with the reference method and with the BD Phoenix System. The inocula were standardized using both the automated (Phoenix AP) and manual (PhoenixSpec) methods. A sufficient number of tests were performed and all quality control results for the BD Phoenix fell within the acceptable ranges demonstrating that the BD Phoenix System can consistently produce quality control results in the recommended range for tigecycline.

Quality control testing of the BD Phoenix – Tigecycline was conducted to demonstrate that acceptable results were achieved >95% of the time by both auto-dilution and manual dilution inoculum preparation methods.

Table 3. Summary of Quality Control Results – BD Phoenix Tigecycline

ORGANISM	Tigecycline (µg/mL)	Reference	Auto-Dilution (Phoenix AP)	Reference	Manual Dilution (Phoenix Spec™)
<i>E. coli</i> Expected Range: 0.03 – 0.25 µg/mL	0.015			1	
	0.03				
	0.06	4			
	0.125	13		98	
	0.25			10	
	≤0.25 [†]		69		105
	0.50				3

[†]BD Phoenix Panel range for Tigecycline is 0.25-16 µg/mL. This dilution range will not cover the full CLSI/FDA-recommended dilution range for QC testing.

Growth Failure Rate: The overall growth rate during the clinical studies was 100%.

Purity Check Plates: Purity check plates were inoculated from the standardized organism suspensions for both the Phoenix and reference methods. Any isolate that showed mixed growth on the purity check plate was considered noncompliant and not included in result

analysis.

Inoculum Density Control: The BD PhoenixSpec Nephelometer was used to prepare the inocula for testing of the clinical, challenge, reproducibility and QC isolates. The same inoculum suspension was used for both the Phoenix System and the reference method testing. The BD Phoenix AP instrument was used to standardize the inocula for challenge, QC, and reproducibility isolates. Validation data for both the PhoenixSpec and the Phoenix AP instrument was provided and found to be acceptable.

d. Detection limit:

Not applicable

e. Analytical specificity:

Not applicable

f. Assay cut-off:

Not applicable

2. Comparison studies:

a. Method comparison with predicate device:

The accuracy of results obtained with the Phoenix System was determined by comparison to the CLSI-recommended broth dilution method (reference method). Reference panels were prepared according to CLSI M07-A8 guidelines. Sites performed testing on gram-negative isolates using Phoenix and reference panel formats appropriate for gram negative organisms. Antimicrobial agents in the test and reference panels had identical dilution ranges which were appropriate for the interpretive breakpoints of the drug. Testing was performed using at least two different production lots of Phoenix panels, AST broth and AST indicator at each study site. A minimum of three different lots of the Phoenix panel were used across all sites for the entire study. Phoenix and reference panels were inoculated using the same organism suspension.

Growth in the Phoenix panels was determined from data recorded by the instrument. Performance was analyzed using FDA breakpoints for tigecycline, and results were compared to results obtained by the broth microdilution reference method based on the guidelines provided in the *Class II Special Controls Guidance Document: Antimicrobial Susceptibility Test (AST) Systems*.

A total of 715 clinical isolates were tested at the three study sites and included both fresh and stock isolates (38 *C. freundii*, 25 *C. koseri*, 15 *Citrobacter spp.*, 34 *E. aerogenes*, 83 *E. cloacae*, 5 *Enterobacter spp.*, 279 *E. coli*, 53 *K. oxytoca*, 131 *K.*

pneumoniae, 4 miscellaneous enteric, 46 *S. marcescens*, 2 *Serratia spp.*) . Stock isolates comprised 34% of total isolates tested. Clinical isolates tested included representatives of species listed in the FDA pharmaceutical drug label. Clinical isolates were tested using inocula prepared using the PhoenixSpec nephelometer (manual method).

A total of 169 challenge isolates were supplied to the testing sites by the sponsor (13 *C. freundii*, 4 *C. koseri*, 1 *Citrobacter spp.*, 14 *E. aerogenes*, 19 *E. cloacae*, 48 *E. coli*, 14 *K. oxytoca*, 30 *K. pneumoniae*, 5 miscellaneous enteric, 17 *S. marcescens*, 4 *Serratia spp.*). Challenge isolates were obtained from BD's internal collection and from external laboratories. Results obtained for Challenge isolates using the Phoenix System were compared to expected MIC results; expected MIC values and categorical interpretations were derived from testing with multiple lots of reference broth dilution panels over a three-month period. The challenge set was divided into subsets and an individual subset was distributed to each of the three study sites. Identification and expected results were masked to the study sites. The inocula for the challenge isolates were prepared using both the PhoenixSpec nephelometer (manual method) and the Phoenix AP (automated method).

The performance evaluation summary of essential and categorical agreement results for clinical, and challenge isolates with inocula prepared using the PhoenixSpec nephelometer (manual method) is shown in the Table 4 below:

Table 4. BD Phoenix Tigecycline (PhoenixSpec Nephelometer - Manual Inoculum Prep)

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#R	min	maj	vmj
Clinical												
<i>Enterobacteriaceae</i>	715	694	97.1	331	320	96.7	698	97.6	2	17	0	0
Challenge												
<i>Enterobacteriaceae</i>	169	168	99.4	77	76	98.7	163	96.4	0	6	0	0
Combined Clinical and Challenge	884	862	97.5	408	396	97.1	861	97.4	2	23	0	0

Table 5. BD Phoenix Tigecycline (Phoenix AP - Auto Inoculum Prep)

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#R	min	maj	vmj
Challenge												
<i>Enterobacteriaceae</i>	170	157	92.4	76	72	94.7	166	97.6	0	4	0	0

EA = Essential Agreement
R = Resistant Isolates
maj = major discrepancies

CA = Category Agreement
min = minor discrepancies
vmj = very major discrepancies

Essential Agreement (EA) occurs when there is agreement between the result of the reference method and that of BD Phoenix within plus or minus one serial two-fold dilution of the antibiotic. Evaluable results are those that are on scale for both the BD Phoenix panel and the reference method. Category Agreement (CA) occurs when the interpretation of the result of the reference method agrees exactly with the interpretation of the BD Phoenix result.

For the clinical and challenge organism testing performed for tigecycline using the BD Phoenix, the overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90%. Overall, there were no major or very major categorical errors and a total of 23 minor errors, the majority of were in essential agreement.

There were no instances of growth failure with either clinical or challenge isolates.

For challenge isolates two methods of organism suspension standardization were used in the evaluation of tigecycline with the Phoenix System. Suspensions were prepared using both the PhoenixSpec nephelometer (manual method) and the Phoenix AP instrument (automated method). A comparison of the performance of the two standardization methods is illustrated in Table 6 below.

Table 6. Comparison of Challenge Isolate Inoculation Standardization Methods

	Tot	EA N	% EA	Total Eval	EA Eval N	%EA Eval	CA N	% CA	#R	min	maj	vmj
Inoculum Method												
PhoenixSpec (Manual)	169	168	99.4	77	76	98.7	163	96.4	0	6	0	0
Phoenix AP (Auto)	170	157	92.4	76	72	94.7	166	97.6	0	4	0	0

For the challenge organisms tested using suspensions prepared with either the manual (PhoenixSpec) method or using the Phoenix AP instrument, the overall % EA and % CA consistently met the acceptance criteria of greater than or equal to 90%. There were 4 minor errors with inocula prepared using the Phoenix AP instrument, and 6 minor errors with inocula prepared using the PhoenixSpec. There were and no very major errors or major categorical errors with either inoculation method.

b. Matrix comparison:

Not applicable

3. Clinical studies:

a. Clinical Sensitivity:

Not applicable

b. Clinical specificity:

Not applicable

c. Other clinical supportive data (when a. and b. are not applicable):

Not applicable

4. Clinical cut-off:

Not applicable

5. Expected values/Reference range:

The MIC interpretive criteria are illustrated in Table 7 below.

Table 7. MIC Interpretive Criteria

Organism	Tigecycline - Susceptibility Interpretive Criteria (MIC in µg/mL)		
	S	I	R
<i>Enterobacteriaceae</i>	≤ 2	4	≥ 8

N. Proposed Labeling:

The labeling is sufficient and it satisfies the requirements of 21 CFR Part 809.10.

O. Conclusion:

The submitted information in this premarket notification is complete and supports a substantial equivalence decision.